UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,827	01/15/2004	Michael R. Rosen	13533/48003	5518

26646 7590 01/21/2010

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
01/21/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,827	ROSEN ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,49,51,57,59 and 65-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,49,51,57,59 and 65-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment to the claims filed September 29, 2009 has been received and entered. Applicants have amended claims 49, 57, 59, 66-67, while claims 1-19, 21-48, 50, 52-56, 58 and 60-64 have been canceled. Applicants have also added claim 69 that is generally directed to elected invention. Claims 20, 49, 51, 57, 59, 65-68 and 69 are pending in this application.

Election/Restrictions

Applicant's election with traverse of the invention of group IV (claims 20, 23-38, 49-50 and 64) filed on October 24, 2005 was acknowledged. Applicant's argument of examining method for treating cardiac condition using composition of for ion channel transfer comprising stem cell modified with a compound (group VI, claim 51-62) with elected group was found persuasive, therefore invention of group IV and VI directed to composition and method of treating cardiac condition were rejoined for the examination purposes.

Claims 20, 49, 51, 57, 59, 65-68 and 69 are under consideration in the instant application.

Withdrawn-Claim Rejections- 35 USC § 112

Claims 49, 57, 59, 66-67 were rejected under 35 U.S.C. 112, first paragraph, because the specification fails to provide an enablement for the full scope of the claimed invention. Applicants' amendments of claims 49, 57, 59, 66, 67-68 and newly added claim 69 address the issue of xenogeneic mesenchymal stem cells transplantation. Therefore, the rejection of claims 49, 57, 59, 66-67 set forth on pp. 3-5 of the previous office action dated April 29, 2009 is hereby withdrawn.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20, 49, 51, 57, 59, 65-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (USP 7,494,644, dated 2/24/2009, effective filing date 11/7/2002), and Qu et al (Circulation res. 2001, 89:e9, IDS).

Claims are directed to a composition comprising a mesenchymal stem cell that is genetically modified with a nucleic acid encoding HCN2. Subsequent claim limit the MSC to include human MSC. Claims are also directed to a method of preparing the composition comprising MSC that is genetically modified to express HCN2 and introducing directly into the heart by injection, wherein MSC form gap junction, thereby treating cardiac rhythm disorder or induce pacemaker current.

With respect to claims 20, 65 and 68, Lee et al teach a composition comprising a recombinant mammalian cell that is genetically engineered to express connexin 43(Cx43) protein intended for establishing electrical coupling between cardiomyocytes and recombinant mammalian cells, wherein the mammalian cells are mesenchymal stem cells. It is reported that the cell may be autologous or allogeneic to the host including human that requires transplantation of genetically modified cell (see col. 14, lines 47-55). Lee et al also teach that Cells may be autologous, allogeneic, or xenogeneic with respect to the host. Thus, teaching of Lee embraces using human mesenchymal stem cell to treat a host that is human (see col. 14, lines 56-60, col. 5, line 21, col. 10, line 8).

Regarding claims 49, 57, 59, 66 and 67, Lee et a teach a method of establishing electrical coupling between cardiomyocytes and recombinant mammalian cells which have been genetically engineered to express a connexin 43 (Cx43) protein, wherein the mammalian cells are mesenchymal stem cells (e.g. claims 1 and 2). It is noted that Lee et al teach that "electrical coupling" means the interaction between cells which allows for intracellular communication between cells so as to provide for electrical conduction between the cells in which electrical excitation of cells through gap junction in the muscle leads to muscle contraction (see col. 10, 20-25). Thus, method of stabling electrical coupling for inducing current is accomplished by injecting MSC to cardiomyocyte in the heart to express the transgene so as to provide for electrical conduction through formation of gap junction meeting the limitation of claims.

Regarding claim 51, Lee et al teach a method for treating a cardiac conduction disturbance in a host, the method comprising: introducing into cardiac tissue of said host a therapeutically effective amount of a recombinant mammalian cell genetically modified to express a connexin 43 proteins; wherein the recombinant mammalian cell is

a mesenchymal stem cell, and wherein the cell is autologous or allogeneic to the host, wherein said introducing is performed by injection into cardiac tissue of the host, or is performed by cardiovascular infusion into the host, and wherein said introducing is effective to establish an electrical connection between the recombinant cell and a myocardial cell of the host cardiac tissue; and wherein the cardiac conduction disturbance in the host is treated (see claim 8). It is noted that in a preferred embodiment Lee et al report that the host is a human. Further, Lee teaches the methods may also be utilized in combination with other cardiac therapies when appropriate.

While Lee et al teach all the limitation of the pending claims, but differed from claimed invention by not disclosing MSC comprising nucleic acid encoding HCN2.

The deficiency of Lee is cured by Qu who reported an adenoviral construct comprising nucleic acid encoding HCN2. Qu et al teach treatment of both adult and neonatal cells in culture with the AdHCN2 construct resulted in expression of high current levels, with faster activation in neonate (Figures 1B and 1C) (see page 2, col. 2, para. 3).

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the composition disclosed by Lee by including the gene of interest HCN2 as disclosed by Qu. One of ordinary skill in the art would be motivated to do use HCN2 as Qu had already shown that HCN2 could be expressed in mammalian cells to induce pacemaker current. One of ordinary skill in the art would reasonably conclude that the composition would implicitly form gap junction when directly administered to the heart of a subject particularly since Lee taught hMSCs engrafts in the myocardium and forms gap junction with recipient MCS (supra). Therefore, given that MSC including human MSC were available for use to express gene of interest as per the teachings of Lee, it would have obvious for one of ordinary skill in the art to include another gene such as HCN2 to produce transformed MSC cells in the method of disclosed by Lee. One who would practice the invention would have reasonable expectation of successfully practicing the composition comprising mesenchymal stem cell incorporated with HCN2 in a method of inducing pacemaker current, forming gap junction or treating rhythm disorder because the art had already shown that hMSC forms electrical coupling with cardiomyocytes and gene or small molecule could be delivered to the heart cells or cardiomyocyte. One of skill in the art would have had a reasonable expectation of success in combining the teachings because Lee et al had already disclosed establishing electrical coupling between cardiomyocytes and genetically modified mesenchymal stem cells, while Qu provided relevant information about a construct comprising HCN2 for inducing pacemaker current in the heart cells. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Response to arguments

Applicants' disagree with the rejection and argue that one of ordinary skill in the art would not be motivated to modify the composition of Lee et al because Lee focuses

on electrical coupling between cardiomyocytes and recombinant cells which have been genetically engineered to express a connexin protein such as connexin 43 (Cx43) proteins. Applicants agree that Lee teaches using stem cells but there is no discussion of transfecting the cells with nucleic acids other than those that encode connexins or with any other purpose than to establish electrical connectivity between the transplanted cells and the heart cells. There is no teaching or suggestion to transfect the cells instead with a different nucleic acid, let alone a nucleic acid encoding HCN and a nucleic acid encoding MiRP 1, for the purpose of altering pacemaker activity. Applicants argue that one of ordinary skill in the art would not have been motivated to modify Lee by replacing the Cx43-encoding nucleic acid of the allegedly disclosed compositions and methods with an HCN-encoding nucleic acid. Applicants further argues that Qu et al. does not cure the deficiency of Lee as it simply attempts to provide an explanation for the observed phenomenon of heterologously expressed HCN2 and HCN4 gene. Applicants further argue that Qu et al do not teach or discuss mesenchymal stem cells or their use to deliver genes to heart (see page 8 and 9 of the arguments).

Applicants' arguments have been fully considered, but are not found persuasive. As an initial matter, applicants should note that claims are directed to a composition comprising "a" mesenchymal stem cell (MSC) incorporated with a nucleic acid which encodes a hyperpolarization activated; cyclic nucleotide gated 2 (HCN2) ion channel, wherein the MSC forms a gap junction with a cell of a mammalian heart. Given the broadest reasonable interpretation in view of the instant specification, claimed composition comprising a MSC is not limited to the expression of HCN2. In fact, claimed composition comprises any MSC that may include a genetically modified or unmodified MSC that is incorporated with HCN2 to create ion channel. Applicants should note that the MSC expressing connexin disclosed by Lee forms gap junction with a mammalian heart cells that could be further used to incorporate HCN2 meeting the limitation of the claim. In addition, prior art teaches administration of MSC in the heart shows growth potential in a myocardial environment and formation of gap junctions suggesting that MSC implicitly forms gap junction with the native cardiomyocytes (see Lee et al and abstract and Figure 6 of Wang et al art of record, not relying for the instant rejection).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., nucleic acid encoding HCN and a nucleic acid encoding MiRP 1) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, if Lee et al had disclosed recombinant cells express HCN2 then this would have been an anticipation rejection and not an obviousness type rejection. In the instant case, it appears that Applicant is arguing that the cited references do not expressly suggest the claimed invention. However, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art is important factors to be considered. The teaching of the cited references must be viewed in light of these factors. Applicants have further engaged in selective reading of the teachings of Lee et al. to formulate the grounds for teaching away.

It should be noted that the ultimate goal of preparing recombinant cell involves implanting cells into myocardial tissue of a subject to establish electrical connection between recombinant and myocardial cell (see col. 3, lines 50-55 of Lee). With respect to applicants' argument that there is no teaching or suggestion in Lee to transfect the cells with a different nucleic acid, it should be noted that Lee et al states that the "recombinant cell can be genetically modified to express other proteins" (see col. 13, line 10). To the extent that Lee et al. describe the composition comprising recombinant MSC capable of forming gap junction that could be genetically modified to express other protein, the rejection is applicable to the instant case (emphasis added). Qu et al teach HCN2 could be expressed in mammalian cells in order to induce pacemaker current in heart. There is no requirement for Qu et al. to teach that which is clearly taught by Lee et al. It should be noted that prior art recognized that hMSC forms electrical coupling with cardiomyocytes and gene could be delivered to the heart cells or cardiomyocyte, while HCN2 over expression induced pacemaker current in mammalian heart. A person

of skill in the art would be motivated to express HCN2 in the recombinant MSC disclosed by Lee, because the method would allow formation of gap junction between recombinant cell and cardiac cell thereby inducing the pacemaker current in the cardiac tissue in the treatment of cardiac rhythm disorder, with a reasonable expectation of success.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Maintained- Double Patenting

Claims 20, 49, 51, 57, 59, 65-66 and 67-69 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12, 39, 65, 67-68, 73-76, of copending Application no 10/342506 (US Patent Publication no 20040137621).

Even though the conflicting claims are not the same, they are not patentably distinct from each other because both sets of claims encompass similar composition and method steps of inducing current and /or treating a cardiac condition by introducing a composition of mesenchymal stem cell comprising a nucleic acid encoding HCN2 into a subject. Claim 20 of the instant application is directed to a composition comprising a mesenchymal stem cell (MSC) incorporated with a nucleic acid which encodes a hyperpolarization activated, cyclic nucleotide gated 2 (HCN2) ion channel in an amount sufficient to create an ion channel in the MSC, wherein the MSC forms a gap junction with a cell of a mammalian heart, wherein MSC is human MSC (claim 68). Claim 49 is drawn to a method of expressing a functional hyperpolarization activated, cyclic nucleotide gated 2 (HCN2) ion channel in a mammalianhuman heart comprising: (1) preparing the composition of claim 68; and (2) site-specifically introducing the composition directly into the heart by injection, microinjection, or catheterization, wherein the MSC forms a gap junction with a cell of the heart. Claim 51 is drawn to a method of treating a cardiac rhythm disorder in a human, wherein the disorder is at least one of conduction block, complete atrioventricular block, incomplete atrioventricular

block or sinus node dysfunction, which method comprises site- specifically introducing directly into the human's heart the composition of claim 68 in an amount sufficient to induce pacemaker current expression at the site, wherein the composition is introduced by injection, microinjection, or catheterization, thereby treating the rhythm disorder in the human. Claim 57 is drawn to a method of inducing a pacemaker current in a human's heart which comprises site-specifically introducing directly into the human's heart the composition of claim 68 in an amount sufficient to induce a pacemaker current in the heart, wherein the composition is introduced by injection, microinjection, or catheterization, and further wherein the MSC forms a gap junction with a cell of the heart, thereby inducing a pacemaker current in the heart. Claim 59 is drawn to a method of inducing a pacemaker current in a human cardiomyocyte which comprises contacting the human cardiomyocyte with the composition of claim 68 in an amount sufficient to induce a pacemaker current in the cardiomyocyte, wherein the composition is introduced by injection, microinjection, or catheterization, and further wherein the cardiomyocyte forms a gap junction with the MSC, thereby inducing a pacemaker current in the cardiomyocyte. Claim 65 is drawn to a composition for delivering a pacemaker current to a mammalian heart comprising a mesenchymal stem cell (MSC) incorporated with a nucleic acid which encodes a hyperpolarization activated, cyclic nucleotide gated 2 (HCN2) ion channel in an amount sufficient to create an ion channel in the MSC and deliver a pacemaker current when site-specifically introduced directly into the heart, wherein the MSC forms a gap junction with a cell of the heart, wherein MSC is a human MSC (claim 69). Claim 66 is directed to a method of inducing a pacemaker current in a human's heart which comprises site-specifically introducing directly into the human's heart the composition of claim 69 in an amount sufficient to induce a pacemaker current in the heart, wherein the composition is introduced by injection, microinjection, or catheterization, and further wherein the MSC forms a gap junction with a cell of the heart, thereby inducing a pacemaker current in the heart. Claim 67 is drawn to a method of inducing pacemaker current in human which comprises contacting the human cardiomyocyte with the composition of claim 69 in an amount sufficient to induce a pacemaker current in the cardiomyocyte, wherein the

composition is introduced by injection, microinjection, or catheterization, and further wherein the cardiomyocyte forms a gap junction with the MSC, thereby inducing a pacemaker current in the cardiomyocyte. It is noted that claims 12, 39, 65, 67-68, 73-76 of copending Application No. 10/342506 are directed to a composition for delivery to a mammalian heart comprising an isolated mesenchymal stem cell incorporated with a nucleic acid encoding at least one hyperpolarization-activated, cyclic nucleotide-gated (HCN) channel, the HCN-encoding region being functionally linked to a promoter, wherein the nucleic acid encoding the at least one HCN channel is expressed, wherein the mesenchymal stem cell further comprises a nucleic acid molecule encoding a MiRP 1 polypeptide. Claim 39 is directed to a method of expressing at least one pacemaker ion channel in a mammalian heart, wherein the at least one pacemaker ion channel is a hyperpolarization- activated, cyclic nucleotide-gated (HCN) channel, comprising (a) preparing the composition of claim 12; and (b) directly administering the composition of claim 12 to the mammalian heart, wherein the the nucleic acid encoding at least one HCN channel encodes a HCN2 channel (claim 65). Claim 67 is drawn to a method for inducing a pacemaker current in a subject's heart comprising: (a) preparing the composition of claim 12; and (b) administering the composition of claim 12 directly to the heart, wherein expression of the pacemaker ion channel in the mesenchymal stem cell generates a pacemaker current in the heart, wherein the nucleic acid encoding at least one HCN channel encodes a HCN2 channel (claim 68). Claim 73 is directed to an isolated mesenchymal stem cell transformed with a nucleic acid encoding at least one pacemaker ion channel, wherein the at least one pacemaker ion channel is a hyperpolarization-activated, cyclic nucleotide-gated (HCN) channel, and wherein the nucleic acid encoding the at least one pacemaker ion channel is expressed, wherein the mesenchymal stem cell further comprises a nucleic acid molecule encoding a MiRP 1 polypeptide, wherein the nucleic acid encoding at least one pacemaker ion channel encodes a HCN2 channel (claim 74). Claim 75 limits the composition of claim 12, wherein the nucleic acid encoding at least one HCN channel encodes a HCN2 channel. Thus, the composition and method set forth in '506. Claims 20, 49, 51, 57, 59, 65-66 and 67-69 are directed to composition and method that is encompassed by the

composition and method set forth in the '506. It is noted that claims in the instant application differ only with respect to a narrower scope of HCN gene, which is encompassed by those specifically claimed in application '506. It is noted that Jansen et al disclose different HCN isoform for the induction of pace maker current. Therefore, it would have been obvious for one of ordinary skill in the art to modify the composition of claim 12 to transfect with HCN2 disclosed by Jansen with reasonable expectation of success in the induction of pacemaker current. Thus, claims 12, 39, 65, 67-68, 73-76of U.S. Patent Application No.: 10/342506 and claims 20, 49, 51, 57, 59, 65-66 and 67-69 of the instant application are obvious over each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Response to arguments

Applicants note that this is a "provisional" rejection over the '506 application, which is not an allowed application. Accordingly, if the now-pending claims of the subject application are otherwise allowable, the present provisional double patenting rejections should be withdrawn and the claims in the subject application should be

allowed and issued, whereby the claims of the '506 application would become subject to an obviousness-type double patenting rejection. Applicants request clarification of this rejection to the extent that it is based on, or "in view of," Jansen et al (See page 9 and 10 of the arguments).

While Applicant has requested that the rejection be withdrawn and allowed whereby '506 would become subject to an obviousness-type double patenting rejection, but a request of abeyance does not overcome or address an issue of obvious double patenting between claims 20, 49, 51, 57, 59, 65-66 and 67-69 in the instant case and application 10/342506. Thus the rejection is maintained. Regarding clarification of Jansen reference, it is noted that instant rejection is not based on the cited references. Claims 20, 49, 51, 57, 59, 65-66 and 67-69 are directed to composition and method that is encompassed by the composition and method set forth in the '506. It is noted that claims in the instant application differ only with respect to a narrower scope of HCN gene, which is encompassed by those specifically claimed in application '506. The Jansen reference was supplied in view of to the extent it would have been obvious for one of ordinary skill in the art to modify the composition of claim 12 and 73 with any of the HCN isoform including HCN2 that is also specifically claimed as dependent claim in '506.

Conclusion

No Claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Pittenger et al (US 6,387,369, dated 2002, ref of record).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Deborah Crouch/
Primary Examiner, Art Unit 1632

Anoop Singh
AU 1632